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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,629	NICOLETTE, CHARLES A.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-11,20 and 25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/17/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 11/29/04 is acknowledged and has been entered.

2. Applicant's election without traverse of Group III (claims 12-24), and species of HLA-A2 and a mammalian tumor epitope is acknowledged.

Claims 12-19 and 21-24 read on the said elected species and are currently being examined.

Accordingly, claim 20 (non-elected species of Group III) and claims 1-11 and 25-29 (non-elected groups I and II) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

3. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example on page 9 at [0038] and on page 20 at [0069]. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

b. In the brief description of the drawings, Figure 3 should disclose "Figure 3 A-D" at [0024].

Appropriate corrections are required.

4. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and

tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12-19 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed composition/kit comprising multiple peptide ligand species directed at a single native ligand, wherein at least two or more peptides activate a different T cell clone from each other and the TCR Vβ recombination of each of the activated T cell clones is different, or different subpopulations of CTL against the same native ligand are activated, including wherein the peptides activate different subpopulations in one member of a selected population of subjects or wherein the peptides activate a different

subpopulation in two or more members of a population of subjects, and including the compositions/kits recited in the instant claims.

The instant claims encompass a composition/kit comprising altered peptide species of unknown structure that function to activate different T cell clones/subpopulations in an individual or between individuals. There is insufficient disclosure in the specification on such a composition/kit comprising the said altered peptide species.

The specification discloses that predictive methods have been developed to scan the sequence of a protein for subsequences that contain a motif for binding to a particular MHC molecule, and that binding can be tested in standard functional assays, or combinatorial peptide and non-peptide chemistry methodologies have provided additional tools for determining T cell epitopes (page 3 at the last paragraph and continuing on to page 4). The specification further discloses that it is possible to improve the effectiveness of natural epitopes by introducing single or multiple amino acid residue substitutions that alter their sequences (page 5 at [0013]). The specification discloses that compositions comprising such altered peptides are useful to modulate an immune response in a subject or to educate naïve immune effector cells (page 6 at [0020]-[0021]). The specification discloses that the altered peptide species are designed and selected to activate an immune response against a native ligand, many of said native ligand(s) will not activate an immune response due to self or peripheral tolerance, and hence said peptide species break tolerance (page 25 at [0091]). The specification discloses that methods to determine Vβ sequence of TCR are known in the art (pages 25-26 at [0093]). The specification discloses that altered gp100 peptide ligands were made and tested for activation of T cells, however, the sequence of the native ligand and the sequence of the altered peptide ligands are not disclosed. The specification discloses that no single altered peptide ligand was immunogenic in every donor, but that there were differential responses suggesting that the T cells each altered peptide ligand preferentially stimulated represented different populations, perhaps with different donor dependent precursor frequencies, and that analysis of Vβ usage within the in vitro educated bulk cultures of normal donor T cells by PCR analysis confirmed this finding (especially pages 63-67). The specification does not disclose what changes were made to the native ligand to produce the altered peptide species and what the correlation was between structure and function of activating different T cell clones/subpopulations of CTLs within individuals or populations.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any native peptide, any MHC, any T cell, in one or more individuals or populations, any altered peptide with an undisclosed structure, and no disclosure between correlation of structure and function is disclosed. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

7. Claims 12-19 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and use the instant invention composition/kit comprising multiple peptide ligand species directed at a single native ligand, wherein at least two or more peptides activate a different T cell clone from each other and the TCR Vβ recombination of each of the activated T cell clones is different, or different subpopulations of CTL against the same native ligand are activated, including wherein the peptides activate different subpopulations in one member of a selected population of subjects or wherein the peptides activate a different subpopulation in two or more members of a population of subjects, and including the compositions/kits recited in the instant claims. The specification has not enabled the breadth of the claimed invention because the claims encompass composition/kit comprising altered peptide species of unknown structure that function to activate different T cell clones/subpopulations in an individual or between individuals. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and used for prophylactically. The specification discloses no working examples with the exception of one, in neither which the structure of the peptides, nor the relationship of the structure to the function is disclosed, i.e., the ability to activate a different T cell clone or a different subpopulation of CTL in an individual or across individuals in a population.

The specification discloses that predictive methods have been developed to scan the sequence of a protein for subsequences that contain a motif for binding to a particular MHC molecule, and that binding can be tested in standard functional assays, or combinatorial peptide and non-peptide chemistry methodologies have provided additional tools for determining T cell epitopes (page 3 at the last paragraph and continuing on to page 4). The specification further discloses that it is possible to improve the effectiveness of natural epitopes by introducing single or multiple amino acid residue substitutions that alter their sequences (page 5 at [0013]). The specification discloses that compositions comprising such altered peptides are useful to modulate an immune response in a subject or to educate naïve immune effector cells (page 6 at [0020]-[0021]). The specification discloses that the altered peptide species are designed and selected to activate an immune response against a native ligand, many of said native ligand(s) will not activate an immune response due to self or peripheral tolerance, and hence said peptide species break tolerance (page 25 at [0091]). The specification discloses that methods to determine Vβ sequence of TCR are known in the art (pages 25-26 at [0093]). The specification discloses that altered gp100 peptide ligands were made and tested for activation of T cells, however, the sequence of the native ligand and the sequence of the altered peptide ligands are not disclosed, nor what the correlation was between structure and function of activating different T cell clones/subpopulations of CTLs within individuals or populations is. The specification discloses that no single altered peptide ligand was immunogenic in every donor, but that there were differential responses suggesting that the T cells each altered peptide

ligand preferentially stimulated represented different populations, perhaps with different donor dependent precursor frequencies, and that analysis of Vβ usage within the in vitro educated bulk cultures of normal donor T cells by PCR analysis confirmed this finding (especially pages 63-67). The specification does not disclose what changes were made to the native ligand to produce the altered peptide species and what the correlation was between structure and function.

Evidentiary reference Anderton (Immunology 2001, 104: 367-376) teaches that in vivo use of altered peptide ligands is unpredictable and dangerous in outbred human populations (especially paragraph spanning columns 1 and 2 on page 370). Anderton further teaches that often T cells are produced in vitro and are dominant in vitro because they are robust enough to withstand the selective pressures of cloning, but they are not representative of the entire in vivo repertoire.

Evidentiary reference Valmori et al (J. Immunol. 1998, 160: 1750-1758) teaches analog peptides that bound to MHC more efficiently than the natural peptide epitope, but which were poorly recognized by tumor reactive CTL, and they could not effectively elicit an immune response against the native antigen or against tumor cells expressing the antigen.

Evidentiary reference Boon (Advances in Cancer Research 1992, 58: 177-210) teaches that establishment of immune tolerance may have already occurred in the patient, and in such cases, active specific immunization will be fruitless, since anergic CTL can not be activated, will not proliferate, and are deficient in effector function (especially page 206 at paragraph 2). Thus, a ligand might stimulate an effective immune response in one patient having a low tumor burden, it may not be immunogenic in another. Accordingly, the skilled artisan can not predict whether each of the peptide analogues of the claimed composition/kit will elicit an immune response against the native epitope or antigen in a patient carrying a large tumor burden, and therefore, the skilled artisan could not use the claimed invention without having to first perform an undue amount of additional experimentation to determine if the analogues are each capable of doing so.

Evidentiary reference Feltkamp et al (Mol. Immunol. 1994 31(18): 1391-1401) teaches that an increased binding affinity for MHC class I molecules does not consistently and reproducibly relate to a peptide's immunogenicity, but that other factors in addition to its binding affinity for MHC determine whether a peptide will be able to stimulate an effective immune response.

Van der Burg et al (J. Immunol. 1996 156(9) : 3308-3314) teaches that the immunogenicity of peptides bound to MHC class I molecules depends on the stability of the complex, not just the binding affinity.

Evidentiary reference Berman et al (J. Virol. 1994 68(8): 5306-5310) teaches failure to induce CTL despite highly efficient recognition in vitro.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 12, 14-19 and 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 12 and 22 are indefinite in the recitation of "multiple peptide ligand species directed at a single native ligand" because it is not clear what is meant.

b. Claims 17 and 18 are indefinite in the recitation of "activate said different subpopulations" because it is not clear what is meant. It is suggested that Applicant amend said claims to recite "activate said different subpopulations of cytotoxic T lymphocytes (CTLs)".

c. Claim 18 recites "said population of subjects". There is insufficient antecedent basis for this limitation in base claim 13.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 12-15, 17-19 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/922,405. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition of '405 is encompassed by the composition of claims 12-15, 19 and 21.

With regard to the limitations recited in instant claims 12, 13, 17 and 18, the ability to activate different subpopulations of CTL, the peptides in the composition of '405 appear to be the same or similar to the peptides in the composition of Application No. 09/922,405 absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of Application No. 09/922,405, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of Application No. 09/922,405.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 16 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/922,405 as applied to claims 12-19 and 21 above and further in view of US 2003/0107092 A1.

Claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, and claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species", limitations that are not present in claims 1-3 of copending Application No. 09/922,405 which are heteroclitic melanoma antigen peptides for HLA MHC.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of Application No. 09/922,405 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 12-15, 17-19 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/931,969. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition of '969 is encompassed by the composition of claims 12-15, 19 and 21.

With regard to the limitations recited in instant claims 12, 13, 17 and 18, the ability to activate different subpopulations of CTL, the peptides in the composition of Application No. 09/931,969 appear to be the same or similar to the peptides of the instant claims absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of Application No. 09/931,969, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of Application No. 09/931,969.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 16 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/931,969 as applied to claims 12-15, 17-19 and 21 above and further in view of US 2003/0107092 A1.

Claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, and claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species", limitations that are not present in claims 1-3 of copending Application No. 09/931,969 which are heteroclitic ovarian tumor peptides for human MHC.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen

for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of Application No. 09/931,969 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 12-15, 17-19 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,737,062 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition of U.S. Patent No. 6,737,062 B2 is encompassed by the composition of claims 12-15, 19 and 21, as they are heteroclitic MHC binding peptides for a human cancer antigen ATF4/CREV-2.

With regard to the limitations recited in instant claims 12, 13, 17 and 18, the ability to activate different subpopulations of CTL, the peptides in the composition of U.S. Patent No. 6,737,062 B2 appear to be the same or similar to the peptides of the instant claims absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of U.S. Patent No. 6,737,062 B2, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of U.S. Patent No. 6,737,062 B2.

16. Claims 16 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,737,062 B2 as applied to claims 12-15, 17-19 and 21 above and further in view of US 2003/0107092 A1.

Claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, and claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species", limitations that are not present in claims 1-3 of U.S. Patent No. 6,737,062 B2 which compositions comprising heteroclitic MHC binding peptides for a human cancer antigen ATF4/CREV-2.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of U.S. Patent No. 6,737,062 B2 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is.

17. Claims 12-15, 17-19 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 10/114,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition of '091 is encompassed by the composition of claims 12-15, 19 and 21, as it comprises p53BP2-related tumor peptides for human MHC.

With regard to the limitations recited in instant claims 12, 13, 17 and 18, the ability to activate different subpopulations of CTL, the peptides in the composition of Application No. 10/114,091 appear to be the same or similar to the peptides of the instant claims absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of Application No. 10/114,091, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of Application No. 10/114,091.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 16 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 10/114,091 as applied to claims 12-15, 17-19 and 21 above and further in view of US 2003/0107092 A1.

Claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, and claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species", limitations that are not present in claims 1-3 of copending Application No. 10/114,091 which are p53BP2-related tumor peptides for human MHC.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of Application No. 10/114,091 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 12-15, 17-19 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/870,216. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition of '216 is encompassed by the composition of claims 12-15, 17-19 and 21, as it comprises heteroclitic ovarian tumor peptides that bind to human MHC.

With regard to the limitations recited in instant claims 12, 13, 17 and 18, the ability to activate different subpopulations of CTL, the peptides in the composition of Application No. 09/870,216 appear to be the same or similar to the peptides of the instant claims absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of Application No. 09/870,216, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of Application No. 09/870,216.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 16 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/870,216 as applied to claims 12-15, 17-19 and 21 above and further in view of US 2003/0107092 A1.

Claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, and claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species", limitations that are not present in claims 1-3 of copending Application No. 09/870,216 which are ovarian tumor peptides for human MHC.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of Application No. 09/870,216 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.
One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 12-15, 17-19 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 40-42 and 49-51 of copending Application No. 09/862,260. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition of 09/862,260 is encompassed by the composition of claims 12-15, 17-19 and 21, as they are heteroclitic melanoma tumor peptides that bind to human MHC.

With regard to the limitations recited in instant claims 12, 13, 17 and 18, the ability to activate different subpopulations of CTL, the peptides in the composition of Application No. 09/862,260 appear to be the same or similar to the peptides of the instant claims absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of Application No. 09/862,260, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of Application No. 09/862,260.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 16 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/862,260 as applied to claims 12-15, 17-19 and 21 above and further in view of US 2003/0107092 A1.

Claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, and claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species", limitations that are not present in claims 40-42 and 49-51 of copending Application No. 09/862,260 which are melanoma tumor peptides for human MHC.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of Application No. 09/862,260 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented, **however it is noted by the Examiner that a notice of allowance has been issued in this application and the issue fee has been paid by Applicant, although a patent has not issued as of this date.**

23. Claims 12-18 and 21-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 09/812,079 in view of US 2003/0107092 A1 and U.S. Patent No. 5,846,827.

Claims 1-6 of copending Application No. 09/812,079 are drawn to individual heteroclitic MHC binding peptides from CMV.

The instant claims are drawn to compositions comprising multiple heteroclitic MHC binding peptides, and instant claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species", limitations that are not present in claims 1-6 of copending Application No. 09/812,079 which are individual heteroclitic CMV peptides for human MHC.

US 2003/0107092 A1 discloses that MHC, or HLA in humans, bind to immunogenic peptides from foreign materials to generate complexes that are recognized by CTL for the purpose of recognizing and acting against the foreign materials. US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0003], [0014], [0101], [0110] and [0111]).

U.S. Patent No. 5,846,827 discloses that viral peptides that bind to MHC class I molecules are useful for activating CTL and for treating viral infections.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of Application No. 09/812,079 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides together in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic peptides in a kit and teaches what the desired immune response to the immunogenic peptides is, and

U.S. Patent No. 5,846,827 discloses that viral peptides that bind to MHC class I molecules are useful for activating CTL and for treating viral infections.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 12-15, 17-19 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34-36 and 43 of copending Application No. 09/812,238.

Claims 34-36 and 43 of copending Application No. 09/812,238 are drawn to compositions comprising heteroclitic MHC binding peptides for a melanoma gp100-associated antigen.

With regard to the limitations recited in instant claims 12, 13, 17 and 18, the ability to activate different subpopulations of CTL, the peptides in the composition of Application No. 09/812,238 appear to be the same or similar to the peptides of the instant claims absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of Application No. 09/812,238, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of Application No. 09/812,238.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claims 16 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34-36 and 43 of copending Application No. 09/812,238 as applied to claims 12-15, 17-19 and 21 above, and further in view of US 2003/0107092 A1 and U.S. Patent No. 5,846,827.

Claims 34-36 and 43 of copending Application No. 09/812,238 are drawn to compositions comprising heteroclitic MHC binding peptides for a melanoma gp100-associated antigen.

The instant claims are drawn to compositions comprising multiple heteroclitic MHC binding peptides, and instant claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species", limitations that are not present in claims 34-36 and 43 of copending Application No. 09/812,238.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers

and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

U.S. Patent No. 5,846,827 discloses that viral peptides that bind to MHC class I molecules are useful for activating CTL and for treating viral infections.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of Application No. 09/812,238 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have produced compositions comprising the peptides and to have packaged the peptides together in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is, and that the peptides may be administered together, and U.S. Patent No. 5,846,827 discloses that viral peptides that bind to MHC class I molecules are useful for activating CTL and for treating viral infections.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 12-15, 17, 18 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 10/283,618.

Claims 1-3 of copending Application No. 10/283,618 are drawn to a composition comprising heteroclitic HIV peptides that bind to MHC in humans.

With regard to the limitations recited in instant claims 12, 13, 17 and 18, the ability to activate different subpopulations of CTL, the peptides in the composition of copending Application No. 10/283,618 appear to be the same or similar to the peptides of the instant claims absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of copending Application No. 10/283,618, the burden is on applicant to show an unobvious distinction

between the composition of the instant invention and that of copending Application No. 10/283,618.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

27. Claims 16, 19 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over copending Application No. 10/283,618 as applied to claims 12-15, 17-19 and 21 above, and further in view of US 2003/0107092 A1 and U.S. Patent No. 5,846,827.

Claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, and claims 22-24 are drawn to a kit comprising the multiple peptide species, and claim 24 recites "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species".

Claims 1-3 of US 2003/0165517 A1 (publication of application serial no. 10/283,618) are drawn to a composition comprising multiple heteroclitic peptides for production of CTL against a native HIV antigen.

US 2003/0165517 A1 (publication of application serial no. 10/283,618) does not disclose wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to the native human ligand, or wherein the peptides are packaged in a kit with instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species, nor the composition of claim 19 wherein the native ligand is a mammalian tumor epitope.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

U.S. Patent No. 5,846,827 discloses that viral peptides that bind to MHC class I molecules are useful for activating CTL and for treating viral infections.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of U.S. Patent No. 6,737,062 B2 to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor

associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is, and U.S. Patent No. 5,846,827 discloses that viral peptides that bind to MHC class I molecules are useful for activating CTL and for treating viral infections.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made heteroclitic versions of the tumor associated antigenic peptides disclosed by US 2003/0107092 A1 instead of the heteroclitic HIV peptides disclosed by US 2003/0165517 A1 (publication of application serial no. 10/283,618).

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer as taught by US 2003/0107092 A1 for compositions comprising tumor antigenic peptides because US 2003/0165517 A1 (publication of application serial no. 10/283,618) discloses the use of heteroclitic peptides to enhance an immune response.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

28. For the purpose of prior art rejections, the filing date of the instant claims 13-19, 21 and 24 is deemed to be the filing date of the instant application, i.e.2/14/02, as the parent application 60/269,077 does not support the claimed limitations of the instant application. The limitations not disclosed in '077 are as follows: "two or more" recited in claim 13 ('077 discloses 2 to 100); ""at least 3 different" recited in claim 15; "naturally contiguous to said native human ligand" recited in claim 16; "in one member of a selected population of subjects" recited in claim 17; "in two or more members of said population of subjects" recited in claim 18; "instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species" recited in claim 24.

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

30. Claims 12-19 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,844,075 as evidenced by US 2002/0169132 A1.

U.S. Patent No. 5,844,075 discloses a native gp-100 melanoma HLA-A2.1 binding ligand G9-209 that consists of the sequence ITDQVPFSV may be modified, such modified peptides may have the general formula $X_1X_2X_3QVPFSX_4$, wherein X1 may be any amino acid, preferably any hydrophobic amino acid, including, but not limited to L, M, A, I, V, T, G, K, F, W, Y, D or S, wherein X_2 is any hydrophobic amino acid, including but not limited to L, M, A, I, V, T or G, wherein X_3 may be any amino acid including D, wherein X_4 may be any hydrophobic amino acid including V. Therefore, U.S. Patent No. 5,844,075 discloses peptides consisting of the sequences wherein X_1X_2 are SF, GV, MT, LI, MV or AI (especially column 25 at lines 29-55). U.S. Patent No. 5,844,075 discloses the consensus sequence in Table 16 is X_1X_2DQVPFSV, i.e., wherein X_3 is D and X_4 is V, and that V is preferred at the carboxy terminus of the peptide (especially column 14 at lines 60-64). U.S. Patent No. 5,844,075 further discloses that the gp100 analog peptides are administered as pharmaceutical compositions in combinations to elicit an immune response in a mammal such as a human HLA-A2 positive subject. U.S. Patent No. 5,844,075 discloses that the analogs include those peptides that exhibit enhanced binding to the MHC molecule with which it is associated when presented to the T cell. U.S. Patent No. 5,844,075 also discloses using flanking amino acid residues present in the native protein (especially claims), and that the proteins or peptides of the invention may be supplied in the form of a kit.

Evidentiary reference US 2002/0169132 A1 discloses gp-100 analog peptides with the consensus motif X_1X_2DQVPFSV, wherein X_1X_2 are SF, GV, MT, LI, MV or AI, and wherein the said peptides have enhanced binding to MHC and enhanced immunoregulatory properties.

With regard to the limitations of the ability to activate different subpopulations of CTL, or a different T cell clone with different TCRVβ recombination, wherein the peptides activate different subpopulations in one member of a selected population of subjects or in two or more members of a population of subjects, the peptides in the composition of U.S. Patent No. 5,844,075 appear to be the same or similar to the peptides of the instant claims absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing composition of the instant invention to those of U.S. Patent No. 5,844,075, the burden is on applicant to show an unobvious distinction between the composition of the instant invention and that of U.S. Patent No. 5,844,075.

31. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

32. Claims 12-19 and 21-24 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,844,075 in view of US 2002/0155447 A1.

U.S. Patent No. 5,844,075 discloses a native gp-100 melanoma HLA-A2.1 binding ligand G9-209 that consists of the sequence ITDQVPFSV may be modified, such modified peptides may have the general formula $X_1X_2X_3QVPFSX_4$, wherein X1 may be any amino acid, preferably any hydrophobic amino acid, including, but not limited to L, M, A, I, V, T, G, K, F, W, Y, D or S, wherein X_2 is any hydrophobic amino acid, including but not limited to L, M, A, I, V, T or G, wherein X_3 may be any amino acid including D, wherein X_4 may be any hydrophobic amino acid including V. Therefore, U.S. Patent No. 5,844,075 discloses peptides consisting of the sequences wherein X_1X_2 are SF, GV, MT, LI, MV or AI (especially column 25 at lines 29-55). U.S. Patent No. 5,844,075 discloses the consensus sequence in Table 16 is X_1X_2DQVPFSV, i.e., wherein X_3 is D and X_4 is V, and that V is preferred at the carboxy terminus of the peptide (especially column 14 at lines 60-64). U.S. Patent No. 5,844,075 further discloses that the gp100 analog peptides are administered as pharmaceutical compositions in combinations to elicit an immune response in a mammal such as a human HLA-A2 positive subject. U.S. Patent No. 5,844,075 discloses that the analogs include those peptides that exhibit enhanced binding to the MHC molecule with which it is associated when presented to the T cell. U.S. Patent No. 5,844,075 also discloses using flanking amino acid residues present in the native protein (especially claims), and that the proteins or peptides of the invention may be supplied in the form of a kit.

U.S. Patent No. 5,844,075 does not disclose the kit that further comprises instructions to coadminister the peptides or to identify subjects who exhibit a positive therapeutic response to the administration of the multiple peptide ligand species, i.e., to the analog peptides.

US 2002/0155447 A1 discloses altering anchor residues (that bind to MHC) of immunogenic peptides from tumor antigens, packaging the peptides in kits, instructions for use (especially [0236] and [0103]-[0104]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included instructions as taught by US 2002/0155447 A1 for the use of tumor analog peptides for the kit taught by U.S. Patent No. 5,844,075 for different tumor analog peptides, i.e., the instructions being to identify subjects who exhibit a positive therapeutic response to the administration of the multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to monitor the therapeutic response to administration of the gp-100 analog peptides disclosed by U.S. Patent No. 5,844,075 because U.S. Patent No. 5,844,075 discloses eliciting an immune response by administering a pharmaceutical composition comprising the said peptides and US 2002/0155447 A1 discloses including instructions for use of a kit comprising immunogenic analog tumor peptides.

33. Claims 16, 19 and 24 are rejected under 35 U.S.C. 103(a) as being obvious over US 2003/0165517 A1 (publication of application serial no. 10/283,618) in view of US 2003/0107092 A1 and U.S. Patent No. 5,846,827.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim 16 recites wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to said native human ligand, and claim 24 is drawn to a kit comprising the multiple peptide species and "further comprising instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species".

Claims 1-3 of US 2003/0165517 A1 (publication of application serial no. 10/283,618) are drawn to a composition comprising multiple heteroclitic peptides for production of CTL against a native HIV antigen. US 2003/0165517 A1 (publication of application serial no. 10/283,618) discloses concatemers of a synthetic antigenic peptide of the invention optionally including intervening amino acid sequences and/or the native ligand as well as polypeptides comprising the sequences (especially [0107]). US 2003/0165517 A1 (publication of application serial no. 10/283,618) discloses that the antigenic peptides of the invention are designed for enhancing binding to MHC molecules and useful for modulating immune responses to the corresponding peptide epitope from which they are derived. US 2003/0165517 A1 (publication of application serial no. 10/283,618) discloses that the

heteroclitic peptides differ from their natural counterparts in that they contain alterations in amino acid sequence, relative to the native sequence, in the MHC class I binding domain which is designed to confer tighter binding to the MHC, and/or they further contain mutations in the putative TCR binding domain designed to increase affinity for TCR, for enhanced immunogenicity (especially [[0098]-[0104]). US 2003/0165517 A1 (publication of application serial no. 10/283,618) discloses that melanoma specific antigen gp100 is a self antigen (especially [0049]). US 2003/0165517 A1 (publication of application serial no. 10/283,618) discloses ways to design and test candidate heteroclitic antigenic peptides.

US 2003/0165517 A1 (publication of application serial no. 10/283,618) does not disclose wherein at least one peptide species is covalently linked to one or more amino acids naturally contiguous to the native human ligand, or wherein the peptides are packaged in a kit with instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species, nor the composition of claim 19 wherein the native ligand is a mammalian tumor epitope.

US 2003/0107092 A1 discloses use of flanking sequences naturally contiguous to the native ligand for HLA (human) MHC binding immunogenic peptides from a tumor associated antigen for use in polytopes, therapeutic compositions comprising pharmaceutically acceptable carriers and the said immunogenic peptides, packaging in kits, and the desired immune response to the said immunogenic peptides (especially [0014], [0101], [0110] and [0111]).

U.S. Patent No. 5,846,827 discloses that viral peptides that bind to MHC class I molecules are useful for activating CTL and for treating viral infections.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have covalently linked at least one peptide species of US 2003/0165517 A1 (publication of application serial no. 10/283,618) to a flanking sequence naturally contiguous to the native ligand as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen, to have packaged the peptides in a kit as disclosed by US 2003/0107092 A1 for peptides from a human tumor associated antigen and to have enclosed instructions to identify subjects who exhibit a positive therapeutic response to the administration of said multiple peptide ligand species.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 2003/0107092 A1 discloses use of flanking amino acid residues to produce polytopes for in vivo administration and further because one of ordinary skill in the art at the time the invention was made would have been aware that flanking sequences naturally present contiguous to the native ligand would facilitate appropriate processing of the peptide(s), and because US 2003/0107092 A1 discloses the utility of packaging immunogenic tumor associated peptides in a kit and teaches what the desired immune response to the immunogenic peptides is, and U.S. Patent No. 5,846,827 discloses that viral peptides that bind to MHC class I molecules are useful for activating CTL and for treating viral infections.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made gp-100 melanoma heteroclitic antigenic peptides as taught by US 2003/0165517 A1 (publication of application serial no. 10/283,618) for HIV peptides. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer as taught by US 2003/0107092 A1 for compositions comprising tumor antigenic peptides because US 2003/0165517 A1 (publication of application serial no. 10/283,618) discloses gp-100 is a melanoma antigen and teaches the use of heteroclitic peptides to enhance an immune response.

With regard to the limitations regarding activation of different subpopulations of CTLs or T cell clones, it is an expected property that the heteroclitic peptides would activate different clones or subpopulations of CTLs since US 2003/0165517 A1 (publication of application serial no. 10/283,618) discloses that the heteroclitic peptides differ from their natural counterparts in that they contain alterations in amino acid sequence, relative to the native sequence, in the MHC class I binding domain which is designed to confer tighter binding to the MHC, and/or they further contain mutations in the putative TCR binding domain designed to increase affinity for TCR.

34. No claim is allowed.

35. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

36. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 4, 2005

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